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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,466	03/01/2002	Alexander Olek	81659A	6657

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,466	OLEK ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-18,20-23,25,26,30-34,36 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-18,20-23,25,26,30-34, 36 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The rejection of claims 1-12, 14-18, 20-23, 25, 26, 30-36, and 41 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in the Office action mailed 03 January 2006 is withdrawn in view of the amendment to the claims filed 05 July 2006.

Claim Rejections - 35 USC § 102

2. The rejection of claims 1-8, 10, 11, 14, 15, 17, 18, 20, 25, 26, 30, 31, and 41 under 35 U.S.C. 102(b) as being anticipated by Kikyo et al. in light of New England Biolabs and Siegfried et al. in the Office action mailed 03 January 2006 is withdrawn in view of the amendment to the claims filed 05 July 2006.

Claims Rejected Under 35 U.S.C. § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al.

The claims are drawn to repeating the method of claim 1 which is drawn to a method of determining differential gene expression, and analyzing methylation states of the gene, wherein the methylation state is determined by use of a bisulfite reaction.

Kikyo et al. shows in the abstract and throughout a method of analysis of mouse embryo tissue for genes that are differentially expressed between normal embryos and abnormal embryos with chromosomal translocations. A differentially expressed neuronatin (Nnat) gene was shown to be imprinted by methylation analysis. Kikyo et al. shows on pages 68-69 differential display analysis of mRNA from the embryos, in which eighty primer pairs were use, and approximately 80-100 bands per primer pair were observed. Ten differentially expressed bands corresponding to differentially expressed genes were observed. Two genes were identified as H19 and Nnat (see figures 1A and 1B). Kikyo et al. further noted on page 69 prior art that used subtraction hybridization to identify Nnat as a differentially expressed gene, and verified Nnat differential expression by a reverse transcriptase-polymerase chain reaction method (see figure 1C). Kikyo et al. subsequently analyzed the Nnat gene for methylation by digestion with a panel of restriction endonucleases Hind III, BssH II, Eag I, and Sac II (see figure 6).

The New England Biolab website establishes that BssH II , Eag I and Sac II enzymes are inhibited by methylation at CpG sites.

Siegfried et al. establishes on page R305 that CpG methylation is a term of art meaning that a cytosine is methylated.

Kikyo et al. does not show repetition of steps or use of a bisulfite reaction to determine methylation states of cytosine.

Frommer et al. shows in the abstract and throughout a method to determine the positions of methylated cytosine residues in DNA by use of sodium bisulfite to convert cytosine to uracil in a chemical reaction (which does not react with methylated cytosine). Frommer et al. shows in page 1828 and figure 1 that their method comprises polymerase chain reactions subsequent to the sodium bisulfite treatment that produces polynucleotides suitable for sequencing reaction analysis. The sequence analysis of the amplified products reveals the presence of positions that originally contained methylated cytosine (see figures 2 and 3). Frommer et al. lists advantages of their method on page 1830, including the positive display of methylated cytosine residues, and the capacity to analyze individual strands of a DNA sample.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to repeat the steps of Kikyo et al. for the purpose of analysis of additional tissue and genes for determination of correlations between expression and methylation, as shown by Kikyo et al. It would have been further obvious to modify the method of Kikyo et al. by use the sodium bisulfite reaction method of methylated cytosine detection of Frommer et al. because Frommer et al. shows that their method also detects methylated cytosine, and has further advantages of positive display of methylated cytosine residues and the ability to analyze individual strands of a DNA sample.

6. Claims 1, 6, 9, 16, 21, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above and further in view of Danssaert et al.

The claims are drawn to the method of claim 1 with the further limitation that the methylation analysis comprises use of a robot or a computer device.

Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above does not show a methylation analysis that comprises use of a robot or a computer device.

Danssaert et al. shows in column 1, lines 22-25 that polymerase chain reactions are best performed on automated devices that allow for consistent thermal cycling. Danssaert et al. shows computer controlled thermal cyclers that comprise robotic arms in column 1, line 33, column 4, and lines 39-50, column 5, lines 31-48.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above by use of a computer controlled thermal cycler, optionally with robotic arms, for conducting the polymerase chain reactions because Danssaert et al. shows that automated thermal cyclers have the advantage of providing consistent thermal cycling, and further because it is obvious to automate a manual activity (see MPEP 2144.04).

7. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. as

applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above, and further in view of Anderson et al.

The claims are drawn to the method of claim 1 with the further limitation that both mRNA and protein levels are measured.

Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above does not show measurement of protein levels.

Anderson et al. shows comparison of human liver gene expression by measurement of mRNA levels and corresponding protein levels (as measured by two-dimensional protein electrophoresis). Anderson et al. shows moderate levels of correlation between mRNA levels and protein levels in figures 1 and 2. Anderson et al. conclude on page 537 that determination of protein levels allows for a better understanding of multi-level gene expression control in complex organisms such as man.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Kikyo et al. as evidenced by New England Biolabs and Siegfried et al. in view of Frommer et al. as applied to claims 1-8, 10, 11, 14, 15, 17, 18, 20, 22, 23, 25, 26, 30-34, and 41 above by additional use of the protein analysis method of Anderson et al. because Anderson et al. shows that determination of correlations between mRNA and protein levels allows for better understanding of gene expression controls.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

John S. Brusca 18 August 2006
John S. Brusca
Primary Examiner
Art Unit 1631

jsb